# Caffeine

CAS #58-08-2
Swiss CD-1 mice, at 0.00, 0.012, 0.025, 0.05% in feed
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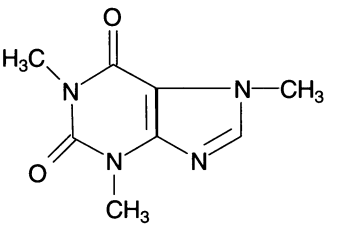


Caffeine, a natural alkaloid drug found in tea, coffee, cocoa, and cola, and a common soft drink additive, was tested for its effects on reproduction and fertility in Swiss CD-1 mice (Morrissey et al., Fundam Appl Toxicol 13:747–777 [1989]). Caffeine was tested simultaneously at two laboratories, each using a variation on the standard RACB study design. This study used Tasks 1, 2, and 4, while the other study in mice utilized Tasks 1, 2, and 3. Caffeine was among the very first compounds run at these labs using this protocol. Data on body weights, clinical signs, and food and water consumptions were collected during the dose-range-finding phase (Task 1), and used to set exposure concentrations for Task 2 at 0.0, 0.012, 0.025, and 0.05% in drinking water. Water was chosen to mimic the route of human exposure. Water consumption was not affected by addition of caffeine. These levels of caffeine, and measured water consumption and body weights, produced calculated consumption estimates of approximately 22, 44, and 88 mg/kg/day.

For the $F_0$ animals, there were no effects on body weight. Alopecia occurred in 55% of the medium dose and 50% of the high dose animals. While there were no exposure-related changes in the number of litters per pair, viability, or adjusted pup weight, the number of live pups per litter, averaged over the four to five litters, dropped 15% at the medium dose and 20% for the high dose animals.

No crossover mating trial was conducted, and the offspring from the last litter of control and high dose mice were reared by their dams until weaning, when they were given the same treatment as their parents until mating at 74 ± 10 days of age.

At the second generation mating trial, there were no changes in any reproductive end point.

At necropsy, at 0.05% level, male body weight was reduced by 8% while male adjusted liver weight increased by 8%. No change was found in female body or organ weights, or in any sperm end point.

In summary, a reduction in the number of live pups per litter for the $F_0$ generation was the only reproductive effect observed in this study. This occurred in the absence of a change in body weights in the $F_0$ parental mice.

**Summary:** NTP Reproductive Assessment by Continuous Breeding Study.

NTIS#: **PB85101202**
Chemical: **Caffeine**
CAS#: **58-08-2**
Mode of exposure: **Drinking water**
Species/strain: **Swiss CD-1 mice**

| $F_0$ generation — Dose concentration → | 0.012% | 0.025% | 0.05% |
|---|---|---|---|
| General toxicity | Male, female | Male, female | Male, female |
| Body weight | —, — | —, — | —, — |
| Kidney weight[a] | • | • | • |
| Liver weight[a] | • | • | • |
| Mortality | • | • | • |
| Feed consumption | • | • | • |
| Water consumption | —, — | —, — | —, — |
| Clinical signs | —, — | ↑, ↑ | ↑, ↑ |
| **Reproductive toxicity** | | | |
| x̄ litters/pair | — | — | — |
| # live pups/litter; pup wt./litter | —, — | ↓, — | ↓, — |
| Cumulative days to litter | — | — | — |
| Absolute testis, epididymis weight[a] | • | • | • |
| Sex accessory gland weight[a] (prostate, seminal vesicle) | • | • | • |
| Epidid. sperm parameters (#, motility, morphology) | • | • | • |
| Estrous cycle length | • | • | • |

| Determination of affected sex (crossover) | Male | Female | Both |
|---|---|---|---|
| Dose level | • | • | • |

| $F_1$ generation — Dose concentration → | • | • | 0.05% |
|---|---|---|---|
| General toxicity | Male, female | Male, female | Male, female |
| Pup growth to weaning | • | • | —, — |
| Mortality | • | • | —, — |
| Adult body weight | • | • | ↓, — |
| Kidney weight[a] | • | • | • |
| Liver weight[a] | • | • | ↑, — |
| Feed consumption | • | • | • |
| Water consumption | • | • | —, — |
| Clinical signs | • | • | • |
| **Reproductive toxicity** | | | |
| Fertility index | • | • | — |
| # live pups/litter; pup wt./litter | • | • | —, — |
| Absolute testis, epididymis weight[a] | • | • | —, — |
| Sex accessory gland weight[a] (prostate, seminal vesicle) | • | • | —, — |
| Epidid. sperm parameters (#, motility, morphology) | • | • | —, —, — |
| Estrous cycle length | • | • | • |

| Summary information | |
|---|---|
| Affected sex? | Unclear |
| Study confounders: | None |
| $F_1$ more sensitive than $F_0$? | No |
| Postnatal toxicity: | No |

Legend: —, no change; •, no observation; ↑ or ↓, statistically significant change ($p<0.05$); —, —, no change in males or females. [a]Adjusted for body weight.